Treatment adherence, efficacy, and safety of etanercept in patients with active psoriatic arthritis and peripheral involvement in Belgium for 66 months (PROVE study)

K. de Vlam[1], C. Boone[2]
and the PROVE Study Group

[1]*Rheumatology, University Hospitals Leuven, Leuven, Belgium;*
[2]*Medical Department, Pfizer SA/NV, Brussels, Belgium*

Abstract

Objective

To describe the long-term adherence, efficacy, and safety in patients with psoriatic arthritis (PsA) treated with etanercept (ETN) in a daily clinical setting in Belgium.

Methods

The PROVE study was a prospective, multi-centre, open-label, observational study in patients with active PsA who had previously failed disease-modifying anti-rheumatic drugs. Patients were treated with ETN prescribed by their physician and adherence was monitored over 66 months.

Results

A total of 303 patients were enrolled (polyarticular-type n=264; oligoarticular-type n=39). 156 (51.5%) patients adhered to the treatment until the end of the study. The mean study duration was 4.0 (SD, 1.9) years. The most common reasons for discontinuing were non-response (35.9%), patient lost to follow-up (20.7%), and reasons unrelated to ETN (20.0%). Males adhered to treatment significantly longer than females (5.0 vs. 3.9 years; p<0.0001). After 6 months, 49.0% of patients with active synovitis at the start of the study had zero joints with synovitis, and this proportion increased to 77.6% by month 66 (p<0.001 for all time points vs. baseline). In polyarticular-type patients, the mean total Health Assessment Questionnaire (HAQ) score (0–60) decreased from 27.0 (95% CI 25.9–28.1) to 9.7 (8.5–10.9; 64.8% improvement; p<0.001) after 6 months and to 7.7 (6.2–9.3; 66.6% improvement; p<0.001) after 66 months. Treatment-related adverse events were reported in 177 (58.8%) of patients, and 53 (17.6%) patients reported serious adverse events related to treatment.

Conclusion

In these patients with active PsA from daily clinical practice, adherence to ETN was high observed over 5.5 years and it was well tolerated.

Key words
psoriatic arthritis, ETN, long-term, adherence, efficacy, safety

Kurt de Vlam, MD, PhD
Caroline Boone,
and the PROVE Study Group

Please address correspondence to:
Kurt de Vlam,
Division of Rheumatology,
University Hospitals Leuven,
Herestraat 49,
B-3000 Leuven, Belgium.
E-mail: kurt.devlam@uzleuven.be

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Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis with a broad range of clinical features including inflammation of the synovium, spine, and entheses, and it is often associated with psoriasis (1, 2). Over time, the inflammation can result in joint or radiographic damage which can severely affect the patient's quality of life (QoL) (3-7). PsA can be classified into 4 categories, with the majority of patients in the clinic presenting polyarticular type (occurring in ≥5 joints), followed by oligoarticular type (occurring in <5 joints) (1). Patients with the oligoarticular type tend to progress to polyarticular type and they are in turn at a higher risk of disease progression (8). Reports of prevalence in the general population vary with estimates calculated at approximately 0.3–1.0% of adults, and this increases to 30% in patients with psoriasis (1, 9). Studies have shown the mortality risk is higher in patients with PsA compared with the general population (10, 11).

Treating PsA can be challenging because often both skin and joint symptoms need to be cared for simultaneously (12). High concentrations of tumour necrosis factor alpha (TNF-α) are found in the synovium and in psoriatic lesions of patients with PsA (13). This led to the introduction of TNF-α inhibitors for treating the disease and they have been shown to be well-tolerated and effective at improving the clinical manifestations of PsA, as well as increasing QoL (14-17).

Past studies have highlighted how the arthritis can dramatically progress if left ineffectively treated (4). Therefore, it is important that patients find a treatment regimen that is not only effective and safe but also one that they will adhere to in the long term. Currently, longitudinal observational studies into treatment adherence of patients with PsA are limited to retrospective or registry data and have concentrated on TNF-α inhibitors as a class rather than focus on individual drugs (18-29). This present study, named PROVE, was performed to evaluate treatment adherence, efficacy, and safety in patients with polyarticular or oligoarticular type PsA treated with the TNF-α inhibitor, etanercept (ETN), over 66 months in clinical practice.

Methods

Study design and patients

PROVE was a Phase IV, prospective, observational, multi-centre, open-label study performed in Belgium. Enrolment started in October 2004 and was to last for 12 months but was extended to December 2006 with a study period of 5.5 years (66 months) to give a total duration of 6.5 years (78 months).

To be included, patients had to be: aged ≥18 years of age, have active PsA, provide written informed consent, and prescribed ETN by their physician or already receiving ETN treatment. In order to be included in the study, patients with erosive polyarticular-type PsA were required to fulfil the Belgian reimbursement criteria for ETN in polyarticular-type PsA of which consisted of: insufficient response to MTX for at least 12 weeks at a minimum dose of 15 mg/week, unless intolerance was documented despite administration of folic acid; presence of active arthritis in ≥5 joints; a health assessment questionnaire (HAQ) total score of ≥25; and absence of active tuberculosis. For patients with erosive or with joint space narrowing oligoarticular-type PsA, they had to fulfil Belgian reimbursement criteria for ETN for oligoarticular-type PsA which comprised of: insufficient response to MTX for at least 12 weeks at a minimum dose of 15 mg/week, unless intolerance was documented despite administration of folic acid; insufficient response or intolerance to non-steroidal anti-inflammatory drugs (NSAID) or sulfasalazine (SSZ); received two local therapy courses (intra-articular) with corticosteroids within the same joint within 3 months unless intolerance was documented; presence of active arthritis in ≥3 joints with at least one joint being a major joint (hips, knee, ankle, shoulder, elbow, or wrist); ≥4 on a numerical rating scale (NRS; 0–10 scale with 10 = worse arthritis) for the most affected major joint completed and signed separately by the patient (NRS patient) and physician (NRS physician); absence of active tuberculosis. Patients were excluded if they had

received investigational drug within 3 months of screening.

Patients attended eight visits in total: baseline and at months 6, 12, 18, 30, 42, 54, and 66. Baseline (Visit 1) occurred within 4 weeks of starting ETN treatment. Visits 2 through 8 were allowed to occur ±1 month of the required date.

This study was conducted in accordance with the International Conference on Harmonisation guideline for good clinical practice and the ethical principles of the Declaration of Helsinki. All patients gave written informed consent, which was reviewed and approved by an independent ethics committee or institutional review board.

Adherence

The proportions of adult patients who adhered to ETN treatment were monitored throughout the study. Patients were withdrawn from the study if any of the followed occurred: lack of patient compliance with the protocol; withdrawal of consent; investigators decision; or sponsor decision. The sponsor could terminate the study at any time for any of the following reasons: failure to enrol patients, protocol violations, inaccurate or incomplete data, unsafe or unethical practices, questionable safety of the current therapy, suspected lack of efficacy of the current therapy, or administrative decision. Kaplan-Meier survival curves were generated for the time in study until withdrawal for the following: all patients, withdrawal due to non-response, withdrawal due to intolerance (defined as adverse events [AEs] or serious AEs [SAEs], by gender, by disease duration class, and by MTX use at the start of ETN treatment.

Efficacy assessments

The number (%) of patients with zero joints with synovitis was calculated during the whole study period. The mean scores (95% confidence intervals [CI]) and percentage improvements from baseline were calculated at each visit for the number of joints with active synovitis, the total Health Assessment Questionnaire (HAQ) score for patients with polyarticular-type PsA, and the NRS patient and NRS physician scores for patients with oligoarticular-type PsA. These assessments were chosen based on the Belgian reimbursement criteria: NRS evaluation for the most affected major joint is requested for oligoarticular-type PsA and the HAQ score is required for the polyarticular-type. The total score for all of the HAQ questions was reported (range 0–60 with higher scores indicating worse quality of life).

Safety

AEs were documented throughout the study. The primary endpoint of the study was the percentage of patients suffering from at least one SAE per year.

Statistical analysis

The statistical software used was IBM SPSS Statistics (v.21.0). No formal sample size calculation was performed prior to the study. The number of patients to be enrolled was determined on the basis of the recruiting capacity of the participating centres within the foreseen recruitment period of 12 months. The estimate for the frequency of patients for whom SAEs are reported during the entire study period was estimated to be approximately 6%, based on data from a previous study (4). The length of the 95% CI was predicted to be between 6.0% and 8.0% for 200 patients and it was concluded that it would be possible to obtain acceptable estimates of the frequency of patients with serious AEs for this number of patients.

The last observation carried forward (LOCF) was determined for the number of joints with active synovitis, the HAQ total, NRS patient, and NRS physician scores. Analyses of variance for repeated measures followed when significant by post-hoc paired Bonferroni's tests were used to compare the HAQ total, NRS patient, and NRS physician scores at all time points versus baseline values. Paired Student's *t*-tests were used to compare the LOCF to the baseline value. Time to withdrawal was illustrated using Kaplan-Meier survival curves. Patients who remained in the study until the last visit or had an unknown withdrawal date were "censored". The mean survival time was determined together with 95% confidence intervals (CIs). Survival curves were compared between independent groups using the log-rank test.

Results

Patient population

Baseline demographics and disease characteristics are shown in Table I. The majority of patients were male (54.8%) with a mean (SD) disease duration of 7.5 (7.4) years and polyarticular-type PsA (n=264; 87.1%). In patients with oligoarticular-type PsA, the knee was the most affected major joint (44.7%). A large proportion of the patients did not receive concomitant MTX (42.9%) and the majority did not take any concomitant oral corticosteroids (73.9%). Patients were given the option of stopping concomitant medication during

Table I. Baseline demographics and disease characteristics.

Characteristic	n=303
Age, years	48.3 (10.8)
Male, n (%)	166 (54.8)
Disease duration, years	7.5 (7.4)
Disease duration by category, n (%)	
≤3 years	110 (37.0)
4–9 years	98 (33.0)
≥10 years	89 (30.0)
PsA type, n (%)	
Poly-articular	264 (87.1)
Oligo-articular	39 (12.9)
Major joint most affected in patients with oligo-articular type, n (%)	38 (100)
Hip	3 (7.9)
Knee	17 (44.7)
Ankle	3 (7.9)
Shoulder	3 (7.9)
Elbow	1 (2.6)
Wrist	6 (15.8)
Knee/ankle	1 (2.6)
Knee/shoulder	2 (5.3)
Knee/elbow	1 (2.6)
Knee/wrist	1 (2.6)
Exposure to treatment, years	3.9 (1.9)
MTX	4.4 (4.2)
SSZ	1.5 (3.0)
Oral corticosteroids	1.5 (3.2)
Concomitant MTX, n (%)	
Taken during entire study	106 (35.0)
Stopped during study	57 (18.8)
Starting during study	10 (3.3)
No concomitant MTX	130 (42.9)
Concomitant SSZ treatment exposure, years	0.1 (0.6)
Concomitant oral corticosteroids, n (%)	
Taken during entire study	32 (10.6)
Stopped during study	31 (10.2)
Starting during study	16 (5.3)
No concomitant oral corticosteroids	224 (73.9)

All values are mean (SD) unless otherwise stated.

Table II. Reasons for withdrawal by treatment period.

Reason	Number of patients (%)							
	≤6 months	6–12 months	12–18 months	18–30 months	30–42 months	42–54 months	54–66 months	Total
Non-response	3 (18.8)	4 (57.1)	15 (53.6)	14 (36.8)	9 (36.0)	6 (27.3)	1 (11.1)	52 (35.9)
Non-serious AE	5 (31.3)	1 (14.3)	5 (17.9)	3 (7.9)	2 (8.0)	2 (9.1)	1 (11.1)	19 (13.1)
SAE	2 (12.5)	1 (14.3)	-	2 (5.3)	1 (4.0)	2 (9.1)	1 (11.1)	9 (6.2)
Patient lost to follow-up	2 (12.5)	-	5 (17.9)	7 (18.4)	6 (24.0)	8 (36.4)	2 (22.2)	30 (20.7)
Reasons not related to ETN	1 (6.3)	1 (14.3)	2 (7.1)	11 (29.0)	7 (28.0)	4 (18.2)	3 (33.3)	29 (20.0)
Non-responder and SAE	1 (6.3)	-	-	1 (2.6)	-	-	-	2 (1.4)
Non-serious AE and patient lost to follow-up	1 (6.3)	-	-	-	-	-	-	1 (0.7)
Non-serious AE and reason not related to ETN	1 (6.3)	-	-	-	-	-	-	1 (0.7)
SAE and death	-	-	1 (3.6)	-	-	-	1 (11.1)	2 (1.4)
Total	16 (100.0)	7 (100.0)	28 (100.0)	38 (100.0)	25 (100.0)	22 (100.0)	9 (100.0)	145 (100.0)*

*Two patients were lost to follow-up and their treatment duration could not be determined and are therefore not present in this analysis.

the study which occurred in 18.8% and 10.2% of patients receiving MTX and oral corticosteroids, respectively.

Adherence

A total of 303 patients started the study and 156 (51.5%) patients adhered to ETN treatment until the end. The mean study duration was 4.0 (SD, 1.9) years. Overall, 145 patients withdrew and two patients were eliminated from the overall population due to the absence of follow-up information after the baseline visit (Table II). The most common reason for withdrawal varied over time: in the first 6 months, non-serious AE was the most common reason for withdrawal (31.3%). The most common reason for withdrawal overall was non-response (35.9%), followed by patient lost to follow-up (20.7%), reasons unrelated to ETN (20.0%), and non-serious AE (13.1%). No patients were withdrawn based on the sponsor's decision. Kaplan-Meier curves were generated to show the probability of remaining in the study for defined groups of patients. For all patients, the mean survival time was 4.5 years before withdrawal (Fig. 1A). When analysing only the patients who withdrew due to non-response (54/303, 17.8% of all patients; 54/145, 37.2% of all withdrawals), the mean time in the study before withdrawal was longer at 5.8 years (Fig. 1B). The number of patients who withdrew due to intolerance was lower (33/303, 10.9% of all patients; 33/145, 22.8% of all withdrawals) and the mean time to study withdrawal was much longer (6.1 years; Fig. 1C). A higher proportion of males (60.8%) *versus* females (40.1%) remained in the study, and the mean time to withdrawal was significantly longer for males (5.0 years *vs*. 3.9 years; $p<0.0001$; Fig. 1D). The mean time to withdrawal was 3.8, 4.7, and 4.8 years for the ≤3 years, 4–9 years and ≥10 years' disease duration groups, respectively (Fig. 1E). The difference was statistically significant ($p=0.029$). A similar number of patients receiving MTX at the start of ETN treatment stayed in the study (49.4%) as those who were not receiving MTX (54.0%) and for a similar length of time ($p=0.533$; Fig. 1F).

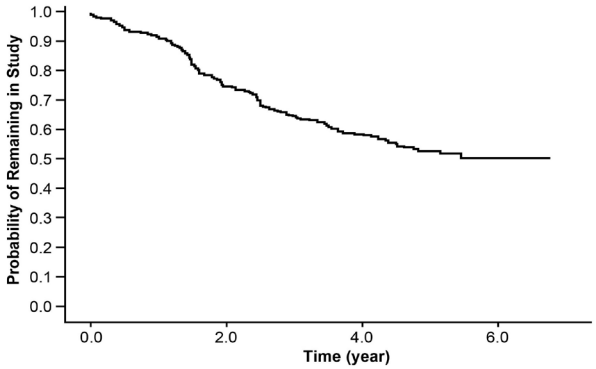
Efficacy

After 6 months of ETN treatment, the number of joints with synovitis significantly improved by 81.7% and this increased to 92.6% by month 66 ($p<0.001$ for all time points; Table III). After just 6 months, 49.0% of patients with active synovitis at the start of the study had zero joints with synovitis, and this proportion continued to increase to 77.6% by month 66 ($p<0.001$ for all time points). In patients with polyarticular-type PsA, HAQ improved significantly from baseline by 66.6% at month 66 ($p<0.001$). In oligoarticular-type patients, the NRS patient score had decreased from baseline by 48.6% by month 66. Similarly, the NRS physician score had decreased by 47.7% from baseline at month 66. All improvements between baseline and all time points were statistically significant ($p<0.001$) for all parameters, with the exception of the NRS patient and NRS physician scores, when month 66 was compared to baseline ($p>0.05$). The differences between baseline and LOCF were statistically significant ($p<0.001$) for all parameters.

Safety

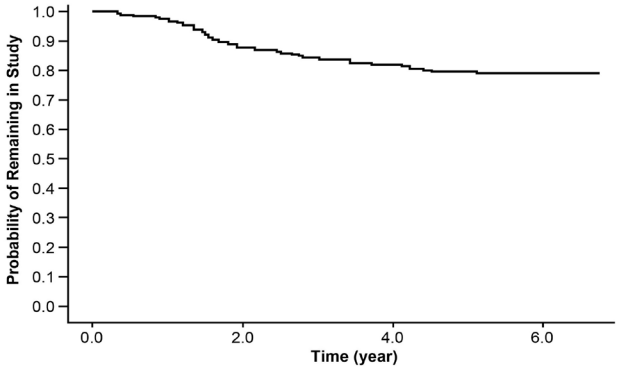
A total of 301 patients were included in the safety population (1184 patient-years up to month 78). The two patients who were lost to follow-up were not included in the safety population. AEs occurred in 67.8% of patients, with 58.8% of patients reporting related AEs (Table IV). The occurrence of AEs was relatively constant across the years of treatment, with 44% of patients reporting at least one AE during year 1 and this decreased to 38%, 34%, 35%, 31%, and 21% during years 2, 3, 4, 5, and 6, respectively. The most commonly reported AEs were nasopharyngitis (n=41; 13.6%), epidermal and dermal conditions (n=28; 9.3%), upper respiratory tract infection (n=24; 8.0%), cough (n=19; 6.3%), headache (n=18; 6.0%), and fatigue (n=18; 6.0%). Injection site erythema, irritation, pruritus, and reaction were experienced by n=1 patients (0.33%) each and injection site rash occurred in n=2 patients (0.66%).All were considered related to the study drug. Five (1.7%)

A) Kaplan-Meier curve of the time in study until withdrawal



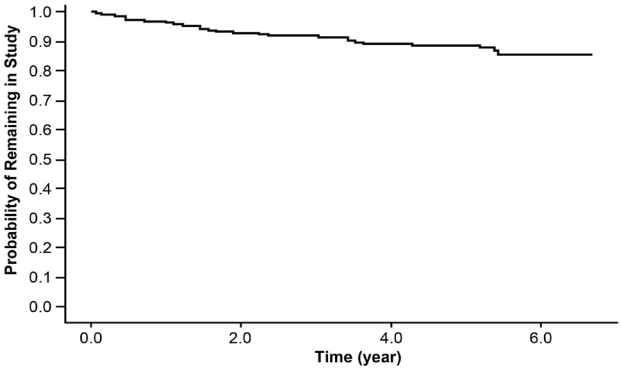
	Total N=303
No. of events	147
Censored, n (%)	156 (51.5)
Mean survival time (95% CI), years	4.5 (4.3-4.8)

B) Kaplan-Meier curve of the time in study until withdrawal due to non-response



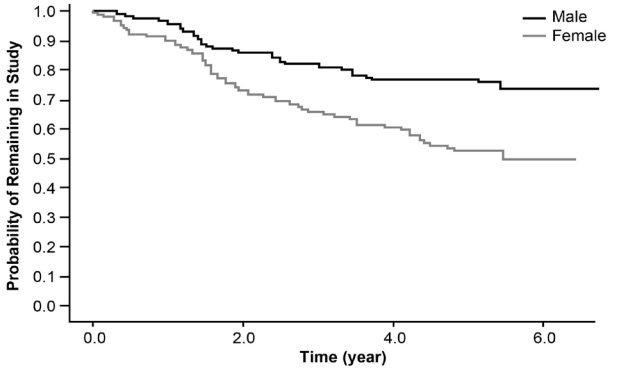
	Total N=303
No. of events	54
Censored, n (%)	249 (82.2)
Mean survival time (95% CI), years	5.8 (5.5-6.0)

C) Kaplan-Meier curve of the time in study until withdrawal due to intolerance



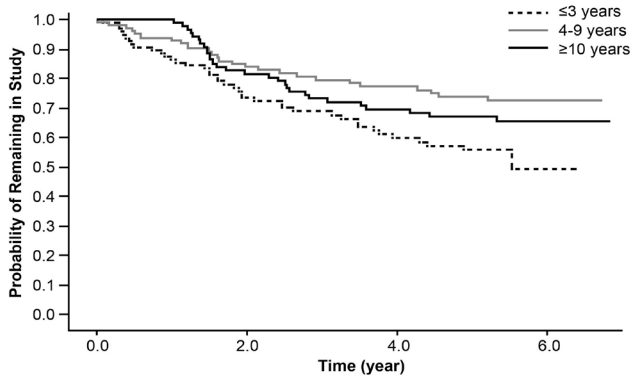
	Total N=303
No. of events	33
Censored, n (%)	270 (89.1)
Mean survival time (95% CI), years	6.1 (5.9-6.3)

D) Kaplan-Meier curve of the time in study until withdrawal by gender



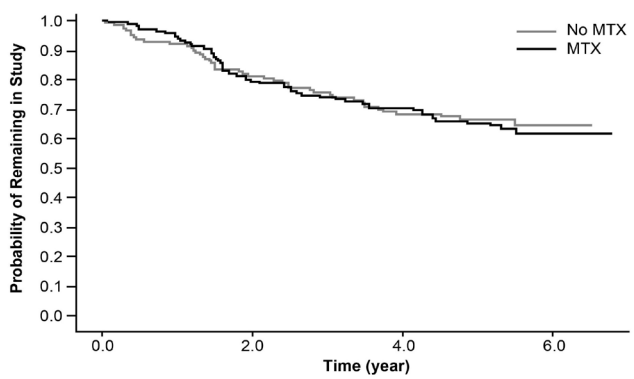
	Male n=166	Female n=137
No. of events	65	82
Censored, n (%)	101 (60.8)	55 (40.1)
Mean survival time (95% CI), years	5.0 (4.6-5.3)	3.9 (3.5-4.3)
p-value	0.000	

E) Kaplan-Meier curve of the time in study until withdrawal by disease duration class



	≤3 years n=96	4-9 years n=103	≥10 years n=88
No. of events	57	43	40
Censored, n (%)	39 (40.6)	60 (58.3)	48 (54.5)
Mean survival time (95% CI), years	3.8 (3.4-4.3)	4.7 (4.3-5.2)	4.8 (4.3-5.2)
p-value		0.029	

F) Kaplan-Meier curve of the time in study until withdrawal by use of MTX at start of ETN



	No MTX n=139	MTX n=164
No. of events	64	83
Censored, n (%)	75 (54.0)	81 (49.4)
Mean survival time (95% CI), years	4.4 (4.1-4.8)	4.5 (4.1-4.9)
p-value	0.533	

Fig. 1. Probability of remaining in the study based on a number of factors.
Censored: patients who had either reached the end of the study or did not have an exact withdrawal date.

Table III. Efficacy outcomes over 66 months.

Visit	All patients (n=303)			Polyarticular patients only (n=264)		Oligoarticular patients only (n=39)	
	No. of patients (%) with 0 joints with synovitis	Mean no. of joints with active synovitis (95% CI)	% improvement from baseline	Mean HAQ total score (95% CI)	% improvement from baseline	NRS patient score	NRS physician score
Baseline	0/302	11.8 (11.0–12.6)	–	27.0 (25.9–28.1)	–	7.4 (6.9–7.8)	6.5 (6.1–6.9)
Month 6	141/288 (49.0)*	2.1 (1.7–2.5)	81.7%*	9.7 (8.5–10.9)	64.8%*	3.3 (2.6–4.1)	2.4 (1.9–3.0)
Month 12	152/260 (58.5)*	1.8 (1.2–2.4)	84.9%*	8.9 (7.5–10.2)	66.9%*	3.2 (2.3–4.0)	2.4 (1.7–3.0)
Month 18	162/261 (62.1)*	1.3 (0.9–1.8)	87.7%*	8.1 (6.8–9.3)	68.4%*	3.3 (2.3–4.3)	2.5 (1.7–3.3)
Month 30	147/215 (68.4)*	1.1 (0.7–1.5)	89.5%*	7.8 (6.5–9.1)	69.4%*	3.0 (2.2–3.8)	2.2 (1.7–2.8)
Month 42	139/189 (73.5)*	0.8 (0.5–1.1)	92.2%*	7.2 (5.8–8.5)	70.7%*	2.2 (1.4–3.1)	1.8 (1.3–2.2)
Month 54	124/169 (73.4)*	0.8 (0.4–1.1)	90.8%*	7.4 (6.1–8.8)	68.5%*	3.1 (1.1–5.1)	2.1 (1.0–3.2)
Month 66	118/152 (77.6)*	0.7 (0.4–1.1)	92.6%*	7.7 (6.2–9.3)	66.6%*	3.8 (0.0–7.6)	3.4 (-0.1–6.9)
LOCF	191/293 (65.2)*	1.5 (0.0–14.0)	87.3%*	9.6 (0.0 – 36.5)	64.4%*	3.3 (1.0 – 8.0)	2.5 (1.0 – 8.0)

*$p<0.001$ *vs*. baseline. LOCF: Last observation carried forward.

cases of leukopenia that were considered related to treatment were reported through the duration of the study: two (0.66%) of these cases were reported in the first 6 months of ETN treatment, and one of each case between 6–12 months, 18–30 months, and 30–42 months.

Table IV. Safety summary at month 66, safety population (n=301).

AEs	Number (%) of patients
AEs, n (%)	204 (67.8%)
Related AEs, n (%)	177 (58.8%)
SAEs, n (%)	65 (21.6%)
Related SAEs	53 (17.6%)
SAEs, System Organ Class	
Cardiac disorders	7 (2.3%)
Ear and labyrinth disorders	2 (0.7%)
Eye disorders	2 (0.7%)
Gastrointestinal disorders	6 (2.0%)
General disorders and administration site conditions	4 (1.3%)
Hepatobiliary disorders	3 (1.0%)
Infections and infestations	13 (4.3%)*
Injury, poisoning and procedural complications	8 (2.7%)
Investigations	1 (0.3%)
Musculoskeletal and connective tissue disorders	11 (3.7%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (1.3%)†
Nervous system disorders	4 (1.3%)
Psychiatric disorders	2 (0.7%)
Renal and urinary disorders	3 (1.0%)
Respiratory, thoracic and mediastinal disorders	7 (2.3%)
Surgical and medical procedures	13 (4.3%)
Vascular disorders	2 (0.7%)

*One case of herpes zoster ophthalmic; †Two cases of rectal cancer and one case each of breast cancer and lung adenocarcinoma metastatic.

Twenty-four (8.0%) patients reported at least one SAE in the first year (primary endpoint). The occurrence of SAEs was relatively constant across the years with 8% of patients reporting at least one SAE in years 1 and 2, and this decreased to 5% in years 3 and 4, and 3% during years 5 and 6. Overall, 237 (78.7%) patients did not report any SAEs during the whole study. Of the 65 (21.6%) patients who reported an SAE, 53 (17.6%) were considered related to ETN. In total, four cases of malignancy occurred during the study: two (0.66%) cases of rectal cancer, one (0.33%) case of breast cancer, and one (0.33%) case of lung adenocarcinoma metastatic. One rectal cancer case and the lung adenocarcinoma metastatic case were considered related to treatment. One of the rectal cancer cases was reported between 6 and 12 months and the other cancer cases were reported after 30 months of treatment. Thirteen (4.3%) patients reported serious infections; these included one (0.33%) case of herpes zoster ophthalmic considered serious and related to treatment.

Discussion

To our knowledge, this is the first prospective long-term study into ETN adherence in patients with PsA. Overall, adherence was considered high: the mean study duration was 4.0 years and 51.5% of patients remained in the study for a period of at least 5.5 years. Based on a Kaplan-Meier analysis in the whole population, the mean survival (adherence to treatment) time was 4.5 years.

The majority of previous longitudinal adherence studies have been shorter in duration and involved patients on a range of TNFα inhibitors. In an analysis of data from a Danish registry (DANBIO) of patients (n=764) on ETN (24%), adalimumab (42%), and infliximab (34%), the median drug survival duration was much lower (2.9 years) than our study despite it being 8 years in duration (20). The 1-year and 2-year survival rates in DANBIO were lower at 70% and 57%, compared with 92% and 75% in our study, respectively. These differences could be due to the different TNF-α inhibitors involved or the fact that this was a Phase IV study and treatment adherence can often be higher when the study is in a more structured format. In addition, the patients had lower disease duration at baseline (median of 5 years compared with 6 years in our study). In a longitudinal observational one-year study into TNF-α inhibitors from a Norwegian registry (NOR-DMARD) of PsA patients (n=172), the 1-year retention rate was also lower at 77.3% (27). The British Society of Rheumatology Biologics Register (BSRBR) and the Spanish BIOBADASER registries had comparable levels of adherence to our data for their respective timeframes (22, 24).

As shown in our study, the main reasons for withdrawal in the aforementioned registry analyses were non-response and AEs (20, 22, 24, 27). Withdrawal due to intolerance was similar to the DANBIO analysis (12% over 8 years represented as % of all patients within

the study) but lower than in the NOR-DMARD (69.2% over one year) and BIOBADASER (45.4% over 3 years) studies (both represented as a percentage of all withdrawing patients). Men were more likely to adhere to treatment than women which echoes the results from the DANBIO, NOR-DMARD, and BSRBR studies (20, 22, 27). A subanalysis of the Southern Swedish Arthritis Treatment Group (SSATG) registry data into patients with PsA (n=261) receiving ETN, adalimumab, or infliximab did not find any connection between gender and drug survival (29). Patients with a longer disease duration (≥4 years) stayed in our study longer than those with a shorter disease duration (<4 years). The reason for this is unknown. The SSATG and BSRBR studies found disease duration did not have an effect on drug adherence.

Concomitant MTX made no significant difference to treatment adherence in our patients, even in the cases of non-response. The BSRBR study also found no significant correlation between concomitant MTX use and study withdrawal, whether it was due to inefficacy or AEs (22). These results differ from the data obtained from the DANBIO, NOR-DMARD, and SSATG studies which all observed that patients receiving concomitant MTX were more likely to stick with TNF-α inhibitor treatment (20, 27, 29, 30).

ETN was effective in reducing the symptoms of synovitis, with the majority of patients still left in the study after 66 months experiencing zero synovitis. The greatest improvement in clinical symptoms occurred within the first 6 months, during which time very few patients withdrew due to non-response (n=3; 18.8% of the total patients who withdrew during that time). After 6 months, inefficacy became the main reason for withdrawal and this was the case for the duration of the study.

Over the five and a half years, ETN was generally well-tolerated. The rate of AEs and infections was comparable to the previous PsA studies and longitudinal registry studies that published safety data in PsA patients (20, 29). The 5-year SSATG study reported SAEs at approximately 5–6% per year in patients with PsA receiving either anti-TNF plus MTX and for those on MTX monotherapy (29). The unusual signal of leukopenia that occurred in five patients would suggest an increased risk of infection but this did not occur in any of the patients. Four instances of cancer were reported, two of which were considered related to treatment.

This study could have been limited by its open-label design; however, the aim of this study was to observe patients in usual clinical practice. Some elements of PsA were not captured, for example, skin or radiographic changes over the five and a half year period. Studies of this length involving PsA patients are limited and this additional information would have been valuable for rheumatologists. New treatment strategies are emerging for PsA in a bid to reduce costs and to minimise toxicities (31, 32). The concept is to treat patients until remission is achieved before reducing or discontinuing the dose whilst retaining remission. Evidence of the effectiveness of this approach in patients with PsA are limited, and the effectiveness of dose tapering and discontinuation were not analysed in the PROVE study. Further long-term studies, both randomised trials and observational studies, which monitor remission whilst adjusting the dose need to be explored.

In summary, the results of this study indicate that ETN is a viable long-term treatment strategy for patients with PsA, and confirm the safety and efficacy profile of ETN when used in daily clinical practice in Belgium.

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